PATENT SPECIFICATION

NO DRAWINGS

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876,009

Date of Application and filing Complete Specification: Nov. 26, 1959.

No. 40221/59.

Complete Specification Published: Aug. 30, 1961.

Index at acceptance:—Classes 2(3), U4(B1: B2: C1: C4: C5); and 81(1), B2Z.

International Classification:—C07c. A61k.

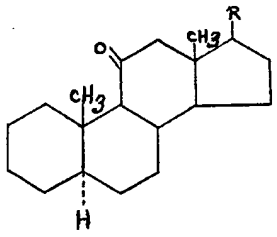
COMPLETE SPECIFICATION

Improvements in or relating to Steroids and the manufacture thereof

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel androstanes, and more particularly to 17 - methyl - 17-hydroxyandrostan - 11 - one and its 17-acylates.

The novel compounds of the present invention can be represented by the following formula:



wherein R is α - methyl - β - hydroxy or α-methyl - β - acyloxy, the acyl radical being that of a hydrocarbon carboxylic acid containing from one to twelve carbon atoms, inclusive. These compounds exhibit a high order of oral anabolic activity and possess the added advantage of having little or no oral androgenic activity at the same dosage level.

3-deoxy steroids are known in the prior art. See, for example, Kochakain, Proc. Soc. Exptl. Biol. and Med., 80, 386 (1952), Am. J. Physiol. 158, 51 (1949), and Inhoffen et al., Ann., 568, 52 (1950). 3 - deoxy - 11 - oxygenated - androstane series steroids are novel, however. In view of the marked loss of activity upon the 11-oxygenation of many hormones, e.g., testosterone, the phsiological activity of the 11-oxygenated steroids of the present invention is particularly surprising. Furthermore, a 3-oxygenated function was heretofore believed vital to the activity of 11-oxygenated steroids.

The 17α - methyl - 17 - hydroxyandrostan-11-one of this invention is to be distinguished from such compounds as the corresponding 11-hydroxy steroid in exhibiting significant anabolic and androgenic activity uncomplicated by the high concomitant central nervous system and neuro-muscular effects characterizing the said 17α - methyl - 11β,17β - dihydroxyandrostane. These novel compounds can be administered in conventional dosage forms such as pills, tablets, and capsules for oral use or in conventional liquid forms as are used with natural and synthetic cortical steroid hormones for injectable preparations.

Raney nickel reduction of the 3-benzyl thioenol ether of 11β - hydroxy - 4 - androstene - 3,17 - dione produces 11β - hydroxy-3,5 - androstadien - 17 - one, which on hydrogenation gives 11β - hydroandrostan - 17-one. Treatment of this compound with the appropriate Grignard reagent yields 17α-methylandrostane - 11β,17β - diol, and 11-oxidation thereof is productive of the novel 17α - methyl - 17 - hydroxyandrostan - 11-one. The said 11-keto product can then be esterified at the 17-position in the usual manner, as with acetic anhydride in pyridine, to give 17α - methyl - 17 - hydroxyandrostan-11-one 17-acylate.

The following examples are illustrative of the products of the present invention and methods for their production but are not to be construed as limiting.

[*Price 3s. 6d.*]

EXAMPLE 1

17α-methylandrostane-11β,17β-diol

A solution of methyl magnesium iodide is prepared by reacting 1 g. of methyl iodide with 290 mg. of magnesium in 20 ml. of anhydrous ether. To this solution is added dropwise a solution of 500 mg. of 11β-hydroxyandrostan-17-one in a mixture of 30 ml. of ether and 12 ml. of benzene. The mixture is stirred in a nitrogen atmosphere for 7 hours and then decomposed by the dropwise addition of a saturated aqueous solution of ammonium chloride. The solution is decanted from the inorganic precipitate, dried and then evaporated to dryness, to leave a residue consisting essentially of 17α - methylandrostane-11β,17β-diol. Chromatography of this product over a column of Florisil (synthetic magnesium silicate) is productive of substantially pure product melting at 178° to 178.5° C. Florisil is a registered trade mark.

EXAMPLE 2

17α-methyl-17-hydroxyandrostan-11-one

A solution of 1 g. of chromic anhydride in 2 ml. of water and 9 ml. of acetic acid was added to 2 g. of 17α - methylandrostane-11β,17β-diol in 30 ml. of acetic acid. The mixture was allowed to stand at room temperature for 1 hour, was diluted with 5—10 ml. of methanol, quenched with water, and chilled to give 1.6 g. of 17α - methyl - 17-hydroxyandrostan - 11 - one, melting point 125 to 128° C. Recrystallization from dilute methanol gave a polymorphic form melting at 157 to 159° C., $[\alpha]_D$ plus 38° in chloroform. When the melt of the lower melting product was seeded with the higher melting material it resolidified and melted at 151 to 157° C. Analysis was as follows:

Calculated for $C_{19}H_{32}O_2$:	C, 78.89;	H, 10.60.
Found:	C, 79.21;	H, 10.75.

EXAMPLE 3

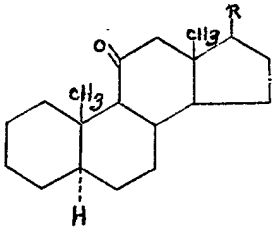
17α-methyl-17-hydroxyandrostan-11-one 17-acetate

A solution of 100 mg. of 17α - methyl - 17-hydroxyandrostan-11-one in a mixture of 1 ml. of acetic anhydride and 1 ml. of dry pyridine is maintained at 80—100° C. for about 4 hours. The excess acetic anhydride is then decomposed with excess ice water and the resulting precipitate filtered and washed with water to give 17α - methyl - 17 - hydroxyandrostan-11-one 17-acetate.

Similarly, other 17 - acylaxy - 17 - methyl compounds are obtained by esterification of the 17β-hydroxy groups, e.g., by reaction with the appropriate acid anhydride, acid chloride or bromide, ester by ester exchange, acid in the presence of an esterification catalyst, etc. Examples of 17β - acyloxy - 17 - methyl-androstan - 11 - ones so obtainable include those wherein the acyl group is the acyl radical of, for example, a lower-aliphatic acid, e.g., formic, propionic, butyric, isobutyric, valeric, isovaleric, trimethylacetic, 2-methylbutyric, 3-ethylbutyric, hexanoic, diethylacetic, triethylacetic, heptanoic, octanoic, α-ethylisovaleric, cyclopropylidene acetic, a cycloaliphatic acid, cyclopentylpropionic, cyclohexylformic, cyclohexylacetic, β-cyclohexylpropionic, an aryl or alkaryl acid, e.g., benzoic, 2-, 3-, or 4-methylbenzoic, 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, and 3,5-dimethylbenzoic, ethylbenzoic, 2,4,6-trimethylbenzoic, 2,4,6-triethylbenzoic, α-naphthoic, 3-methyl - α - naphthoic, an aralkyl acid, e.g., phenylacetic, phenylpropionic, diphenylacetic, triphenylacetic etc.

WHAT WE CLAIM IS:—

1. Compounds of the following formula:

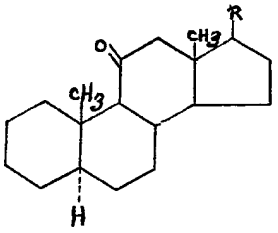


wherein R is α - methyl - β - hydroxy or α-methyl - β - acyloxy, the acyl radical being that of a hydrocarbon carboxylic acid containing from one to twelve carbon atoms, inclusive.

2. 17α - methyl - 17 - hydroxyandrostan-11-one.

3. 17α - methyl - 17 - hydroxyandrostan-11-one and 17-acetate.

4. A process for the preparation of compounds of the following formula:



wherein R is α - methyl - β - hydroxy or α-methyl β - acyloxy, the acyl radical being that of a hydrocarbon carboxylic acid containing from one to twelve carbon atoms inclusive, which comprises: reacting 11β-hydroxyandrostan - 17 - one with a methyl

magnesium halide to obtain 17α - methyl-androstane - 11β,17β - diol, oxidizing the said 17α-methyl steroid to give the corresponding 17α - methyl - 17 - hydroxyandrostan-11-one, and, if desired, acylating the said 17α-methyl-17-hydroxy steroid with an acylating agent containing from one to twelve carbon atoms, inclusive, to produce the corresponding 17α - methyl - 17 - hydroxyandrostan - 11-one 17-acylate.

5. A process for the preparation of 17α-methyl - 17 - hydroxyandrostan - 11 - one which comprises: reacting 11β - hydroxy-androstan - 17 - one with methyl magnesium iodide to obtain 17α - methylandrostane-11β,17β-diol, and oxidizing the said 17α-methyl steroid with chromic anhydride and acetic acid to give the said 17α - methyl - 17-hydroxyandrostan - 11 - one.

6. A process for the preparation of 17α-methyl - 17 - hydroxyandrostan - 11 - one 17-acetate which comprises: reacting 11β-hydroxyandrostan - 17 -one with methyl magnesium iodide to obtain 17α-methylandrostane-11β,17β-diol, oxidizing the said 17α-methyl steroid with chromic anhydride and acetic acid to give 17α - methyl - 17 - hydroxyandrostan-11-one, and acetylating the said 17α - methyl-17-hydroxy steroid with acetic anhydride in pyridine to produce the said 17α - methyl - 17 - hydroxyandrostan - 11 - one 17 - acetate.

7. A process as claimed in claim 4, wherein 11beta - hydroxyandrostan - 17 - one is prepared by Raney nickel reduction of 3-benzyl thioenol ether of 11beta - hydroxy - 4 - androstene - 3,17 - dione and hydrogenation of the resulting 11beta - hydroxy - 3,5 - androstadien-17-one.

8. 17alpha-methylandrostane-11beta,17beta-diol.

9. A process for the preparation of 17alpha-methylandrostane - 11beta,17beta - diol which comprises treating 11beta - hydroxyandrostan-17-one with a methyl Grignard reagent.

10. A process for the preparation of a novel steroid according to claim 1 substantially as herein described with reference to any of the Examples.

11. A novel steroid according to claim 1 when prepared by a process as claimed in any of claims 4 to 7, 9 or 10.

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Chartered Patent Agents,
51/52 Chancery Lane, London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1961.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.